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Reports

Importance of Supplemental Vitamin C in Determining Serum Ascorbic Acid in Controls From a Cervical Cancer Case-Control Study: Implications for Epidemiological Studies

Rashmi Sinha, Carolin M. Frey, William G. Kammerer, Mary J. McAdams,
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Abstract

Classification of individuals by their vitamin C intake was investigated in 493 control subjects from a cervical cancer case-control study. The influence of dietary and supplemental sources of vitamin C, as well as demographic and life-style factors, on serum ascorbic acid were examined. Usual dietary intakes of vitamin C were determined from a food frequency questionnaire and recent intakes from a 24-hour recall taken at the time of blood collection. Vitamin supplement information was obtained at both times. In a regression analysis, the factors found to predict serum ascorbic acid were total recent vitamin C intake, an indicator variable for supplement use, body mass index, number of cigarettes smoked per day, race, education, and age. Higher levels of serum ascorbic acid were found among older nonsmoking highly educated leaner white women. Consideration of supplements, in addition to dietary sources of vitamin C, improved correlation coefficients between serum ascorbic acid and usual vitamin C intake from 0.19 to 0.32 and between serum ascorbic acid and recent intake from 0.36 to 0.56. Furthermore, whereas only a twofold difference between the first and fourth quartiles of serum ascorbic acid was observed using recent dietary vitamin C without supplements, this range increased to sixfold with addition of supplement data. Epidemiological studies should consider use of total vitamin C intakes from supplement and food sources to permit accurate classification of individuals.

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Introduction

Vitamin and mineral supplements may contribute substantially to overall nutrient intakes for certain population subgroups (1). The National Health Interview Survey (HIS), when categorizing by race and gender, reports that, among 55- to 64-year-old individuals, 40% of white women, 27% of white men, 21% of black women, and 18% of black men consume supplements every day (2). Supplemental sources are especially important for vitamin C, because 85-90.6% of those taking supplements use this vitamin and take it more frequently than any other single supplement (1,3).

Many studies described the protective role of vitamin C in certain types of cancers (4-8), but few epidemiological studies have evaluated the role of supplemental vitamin C, possibly because of difficulties in obtaining detailed and accurate information on supplement use. Block and co-workers (9) found that, of 110 US cancer epidemiological studies, information on vitamin supplements was obtained in only 27. This may lead to misclassification of an individual's true nutrient status at the level of estimated intake and tissue concentration, leading to bias in risk estimates.

We took advantage of detailed information on supplement use collected in a cervical cancer case-control study to look at the contribution of supplements to total dietary intake and blood levels of vitamin C, such that we could examine the degree of misclassification if only dietary vitamin C was used compared with total vitamin C consumed. Moreover we also evaluated the effects of other variables, such as age, race, education, smoking, and alcohol use, on the relationship between intake of vitamin C and serum ascorbic acid (AA).

Methods

This study analyzed data from control subjects participating in a case-control study of cervical cancer carried out during 1982-85 (10,11). Up to two control women (median age 44 yrs) individually matched to cases on five-year age group, race, and neighborhood were identified through random-digit dialing techniques (12,13). Blood samples were obtained from 361 white (72% of those interviewed) and 132 black (56% of those interviewed) subjects. Hispanics, Asians, or subjects of unknown race (8% of those who gave blood) were excluded from analyses.

As part of the standardized interviews about cervical cancer risk factors, a food frequency questionnaire (FFQ) was administered to study subjects by a trained interviewer. Dietary intake was assessed by asking about "usual adult frequency of consumption, ignoring any recent changes," of 75 food items (10,11). Included were the major dietary sources of carotenoids, vitamin A, vitamin C, and folate in the diets. Subjects were asked to respond in terms of numbers of servings per day, week, month, or year.

Also, as part of the standardized interview, information on usual adult use of vitamin supplements was obtained by asking "before one year ago, did you take any of the following vitamin pills or supplements on a regular basis." Specifically probed were use of multivitamins (type and brand were obtained wherever possible), vitamin A, vitamin C, vitamin E, folic acid, carotene, yeast, wheat germ, and fish liver oil. The subjects were asked for how many years during the last 20 years they had taken each supplement and how often they took the supplement when they were using it. For vitamin C, subjects were asked the daily dosage. The questionnaire also elicited detailed information on demographic characteristics, smoking, familial medical history, and other cervical cancer risk factors.

Blood (40 ml) was collected from each study subject after (median elapsed time 6.7 mos) the initial questionnaire. The Vacutainer tubes were allowed to sit upright at room temperature for 40-60 minutes. The serum was separated, and 1 ml was immediately mixed with 1 ml of freshly made 10% metaphosphoric acid to stabilize the AA. Samples then were stored at -70°C

for later AA assay using 2,4-dinitrophenylhydrazine as chromogen (14). This assay measured the reduced and oxidized or dehydro forms to give total AA.

At blood collection, a brief questionnaire that gathered information on foods and beverages consumed recently, that is, in the past 24 hours, was also administered, with emphasis on vitamin C-rich items. Recent dietary vitamin C intake was estimated using the US Department of Agriculture working version of the survey nutrients data base (January 1991).

Detailed information on recent (in the last month) vitamin supplement use was obtained at the time the blood was drawn. The type and brand names of any multivitamins and daily dose of specific single vitamins (i.e., vitamins A, C, and E, folic acid) were elicited whenever possible. The subjects were asked to respond in terms of numbers of times per day or week they took the supplements. Information on medications and smoking in the last month as well as within the last 24 hours was also ascertained.

All multivitamin supplements were coded with their brand names or type (e.g., one-a-day, stress). The vitamin C content of those with brand names were assigned amounts from information provided by the manufacturer. Where the brand name was missing but the multivitamin type was indicated, the quantities assigned were 60 mg for one-a-day-type tablets, 200 mg for therapeutic, and 600 for stress-type tablets. Where the brand and the type of multivitamin was missing, 60 mg of vitamin C were assigned. For single vitamin C supplements, the dose assigned was as indicated by the subject in the questionnaire. If the dosage of a single vitamin C supplement was not provided, it was assigned 500 mg (the modal dosage for vitamin C supplement use found by the Gallup study) (15,16). There was incomplete information on supplemental vitamin C from multivitamin or single supplement for 44 subjects for usual and 5 subjects for recent questionnaire. The vitamin C supplement information for these subjects was flagged, and the data were analyzed for "all subjects" as well as "nonflagged subjects."

The basis for statistical model development for determinants of serum AA first required choosing a measure of dietary intake of vitamin C. Four measures of vitamin C intake were evaluated: "recent" dietary intake from 24-hour recall, "usual" dietary intake from FFQ, "total (dietary and supplemental) recent" intake from 24-hour recall, and "total (dietary and supplemental) usual" intake from FFQ. Spearman correlations were used to compare the degree of association between each of the four possible intake measures and serum AA. Because of skewing, vitamin C intakes were logged to the base 10 in subsequent regression analyses.

Regression analyses were used to evaluate possible contributions of a variety of factors to the relationship between vitamin C intake and serum AA. The demographic variables examined were race, age, study site, income, and education. Other plausible biologic factors investigated were weight, body mass index (BMI), season when blood was drawn, time of day blood was drawn, day of the week blood was drawn, hours since last meal when blood was drawn, medication taken in the last month, alcohol intake, smoking status, and smoking intensity. Each potential covariate was evaluated in a separate regression model for serum AA, which already included the logged measure of vitamin C intake. The statistically significant (F statistic, $p < 0.05$) variables at this stage were retained for evaluation of two-way interactions. For example, the interaction of vitamin C intake with race compared the model consisting of $\log(\text{total vitamin C intake}) + \text{race} + \log(\text{total vitamin C intake}) \times \text{race}$ to the model with only $\log(\text{total vitamin C intake}) + \text{race}$. With this approach, the final model for predictors of serum vitamin C was developed.

Results

Figure 1 illustrates the distribution of serum AA levels from the controls of the present cervical cancer case-control study compared with the age-specific data from the Second National Health and Nutrition Examination Survey (NHANES II) conducted in 1976-80

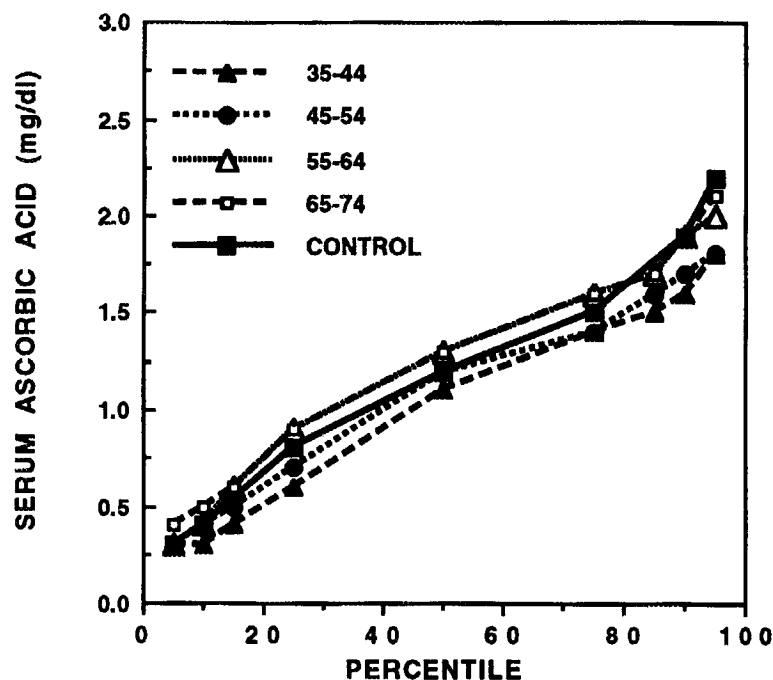


Figure 1. Mean serum ascorbic acid levels within selected percentiles for females of different ages from NHANES II and controls of cervical cancer case-control study.

(17). Controls from the cervical cancer case-control study were within the range of AA levels found in the NHANES II for women with similar ages.

Vitamin C intake characteristics for study subjects are shown in Table 1. Subjects were divided into non-supplement users or supplement users for usual and recent estimates of vitamin C intake. In this study, subjects were considered to be supplement users if they were taking ≥ 30 mg of vitamin C per day (equivalent of One-a-Day multivitamin at least every other day); 46% of the subjects were categorized as usual vitamin C supplement users, because they were taking vitamin C on a regular basis sometime over the last 20 years; 34% consumed vitamin C containing supplements in the last month.

The median usual intake of dietary vitamin C was similar between the non-supplement users and supplement users, but the total intake was 3.5 times greater for the supplement users. There was, however, somewhat higher recent dietary intake of vitamin C in recent supplement users than in non-supplement users. The difference between the supplement users

Table 1. Median Vitamin C Intake Among Supplement and Non-Supplement Users^a

	<i>n</i>	% of Subjs	Median Vitamin C, mg/day		
			Diet	Supplement	Total
Usual intake: FFQ ^b					
Non-supplement user	268	54	139	0	139
Supplement user	225	46	143	310	486
Recent intake: 24-hr recall					
Non-supplement user	323	66	50	0	54
Supplement user	170	34	79	169	278

a: Subjects were considered to be supplement users if they were taking ≥ 30 mg of vitamin C per day (equivalent of One-a-Day multivitamin at least every other day).

b: Food frequency questionnaire.



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and non-supplement users was accentuated when total recent vitamin C intake was compared; supplement users consumed approximately five times more total vitamin C than non-supplement users.

The distribution of subjects by quartiles for dietary vitamin C and total (diet plus supplement) vitamin C intake was compared (Table 2). There was an overall agreement between the two sets of quartiles of 42% for the usual intake and 52% for recent intake of vitamin C. Ten percent of the subjects for usual vitamin C intake were not in the same or adjacent quartiles when the two distributions were compared. For the recent vitamin C intake, 8% of the subjects were two or more categories away from the diagonal.

The correlation between usual and recent dietary vitamin C intake was low (Table 3). However, adding supplemental vitamin C to dietary vitamin C increased the observed correlation from 0.18 to 0.40. Furthermore the correlation between usual dietary vitamin C and serum AA was found to be 0.19 and improved to 0.32 with the addition of usual supplement intake. Serum levels are more responsive to recent intake of this vitamin, and a correlation of 0.36 was found between recent dietary vitamin C intake and serum AA. When recent intake of supplemental vitamin C was added to recent dietary intake estimates, the correlation increased to 0.56.

Serum AA was stratified into quartiles, and mean dietary, supplemental, and total vitamin C intakes were determined within each quartile for the usual and recent vitamin C intake.

Table 2. Comparison of Quartile Distribution by Dietary Vitamin C Alone and by Total (Diet + Supplement) Vitamin C				
Quartiles of Total (Diet + Supplement) Vitamin C	Quartiles of Diet Vitamin C ^a			
	1st	2nd	3rd	4th
<i>Usual intake: FFQ</i>				
1st	17	8	0	0
2nd	3	10	12	0
3rd	1	2	6	16
4th	5	4	7	9
<i>Recent intake: 24-hr recall</i>				
1st	18	7	0	0
2nd	3	12	10	0
3rd	1	2	9	12
4th	3	4	6	13
a: Values are percentages.				

Table 3. Spearman Correlation Coefficients for Vitamin C Intake and Serum Ascorbic Acid ^a	
Correlation	Coeff ^b
Usual diet vitamin C and recent diet vitamin C	0.18
Usual diet vitamin C + usual supplement vitamin C and recent diet vitamin C + recent supplement vitamin C	0.40
Usual diet vitamin C and serum ascorbic acid	0.19
Usual diet vitamin C + usual supplement vitamin C and serum ascorbic acid	0.32
Recent diet vitamin C and serum ascorbic acid	0.36
Recent diet vitamin C + recent supplement vitamin C and serum ascorbic acid	0.56
a: n = 493.	
b: All correlations significant (p < 0.05).	

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Supporting the correlational data, Figure 2 suggests that usual intake of dietary vitamin C does not predict serum AA very well and that the increase in serum AA is due mainly to supplemental intake of vitamin C. Similarly, recent supplemental vitamin C intake plays a greater role in increasing serum AA than recent dietary intake (Figure 3), even though there is a slight dose relationship between mean recent dietary intake of vitamin C and the quartiles of serum AA.

Figure 4 is a scatter plot for total vitamin C intake by serum AA with unadjusted slopes for white and black women. Figure 4 shows that there are more white women with higher total intake of vitamin C and higher serum AA levels than black women. Because there are fewer black women consuming high levels of vitamin C, it is difficult to assess the significance of race-specific slopes.

Linear regression analysis, as described in **Methods**, was used to predict serum AA from logged recent total vitamin C intake. The choice to use this measure of vitamin C intake was based on its higher Spearman correlations with serum AA (Table 3) than the other proposed measures. Beyond intake, race appeared to be the predominant predictor of serum AA contributing significant incremental terms for slope and intercept. To this basic model, covariate terms, as noted above, were tested and included in the final model if judged significant at the 0.05 level. Table 4 shows estimates of terms included in the best predictive model for serum AA from this data set.

The main determinant of serum AA was total reported vitamin C intake in the last 24 hours, which accounted for 0.289 of the total R^2 (Table 4). The incremental slope for blacks

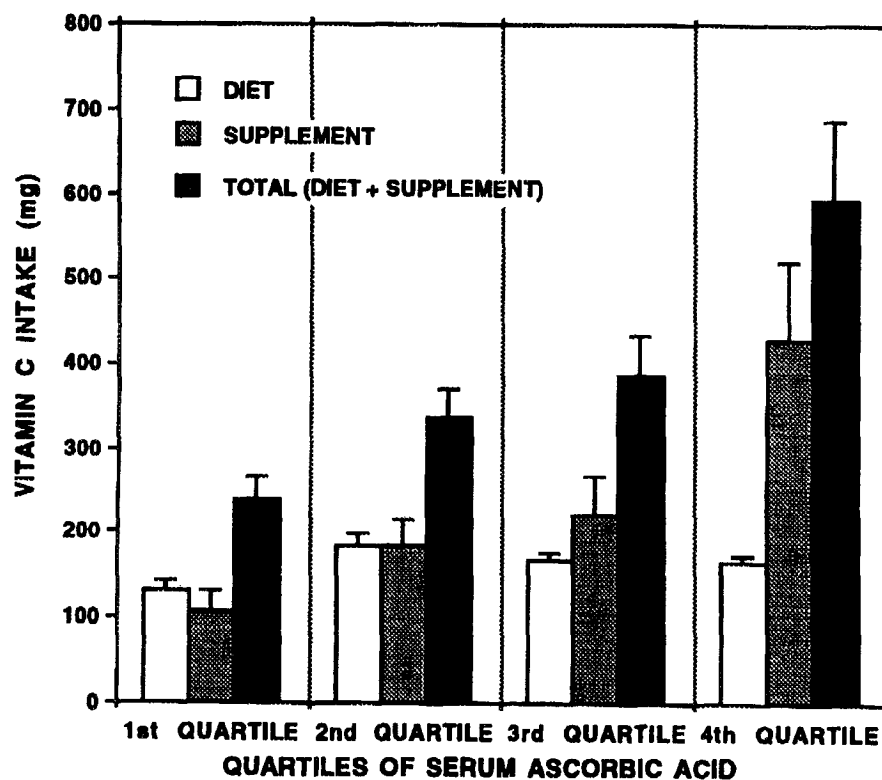


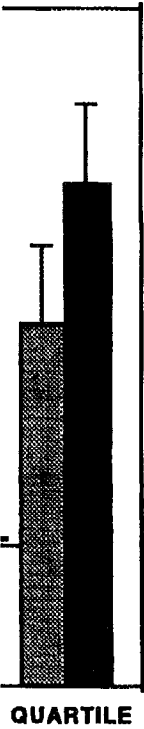
Figure 2. Mean usual vitamin C intake estimates from diet, supplement, and total within quartiles of serum ascorbic acid. Ranges of serum quartiles are as follows: 1st, 0.07–0.78 mg/dl; 2nd, 0.79–1.23 mg/dl; 3rd, 1.23–1.54 mg/dl; 4th, 1.55–3.90 mg/dl.

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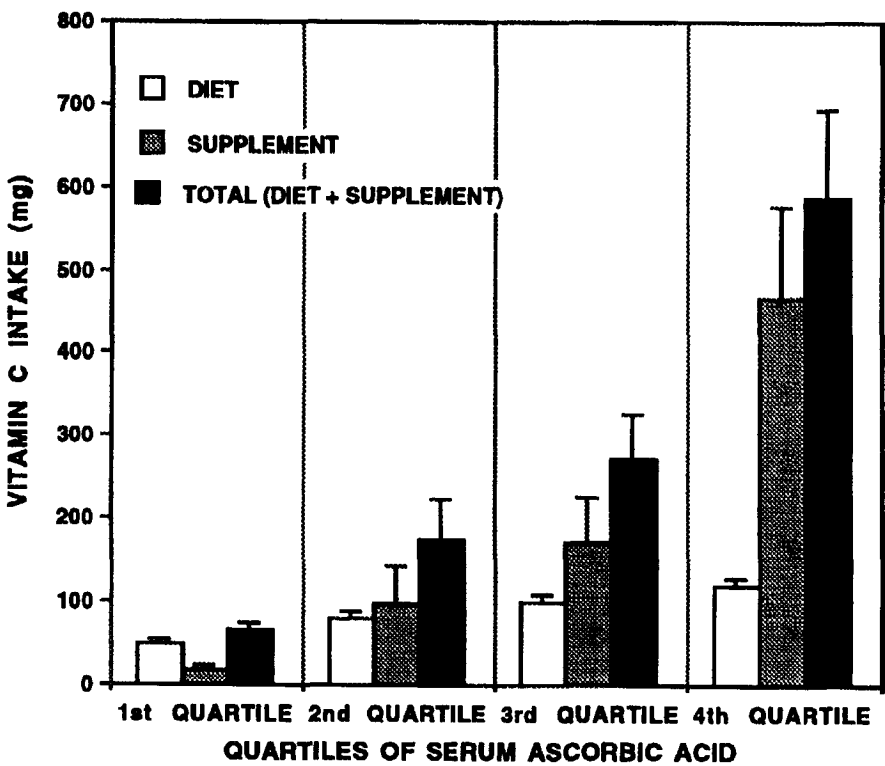


Figure 3. Mean recent vitamin C intake estimates from diet, supplement, and total within quartiles of serum ascorbic acid. Ranges of serum quartiles are as follows: 1st, 0.07–0.78 mg/dl; 2nd, 0.79–1.23 mg/dl; 3rd, 1.23–1.54 mg/dl; 4th, 1.55–3.90 mg/dl.

Table 4. Influence of Total Recent Vitamin C Intake, Supplement Use, BMI, Cigarettes Smoked, Race, and Age on Serum Ascorbic Acid by Use of Regression Analysis				
	β Coeff ^a		P Value	R ²
Basic model				
Total recent vitamin C intake ^c (slope)	0.40	(0.05)	0.0001	0.405 ^b
Increment in slope for blacks ^d	-0.22	(0.06)	0.0009	0.289
Increment in intercept for blacks	0.23	(0.13)	0.07	0.041
Covariates				
Supplement use ^e	0.20	(0.06)	0.0003	0.024
Cigarettes/day ^f	-0.16	(0.06)	0.004	0.014
BMI ^g	-1.42	(0.44)	0.001	0.011
Age (yrs)	0.005	(0.002)	0.001	0.010
Education ^h	0.21	(0.07)	0.002	0.011

a: Value in parentheses is SE.
b: Total R²; all other values are partial R².
c: Vitamin C intake in mg was log₁₀ transformed.
d: Race (indicator variable): white, 0; black, 1.
e: Indicator variable for supplement users and non-supplement users.
f: Cigarettes smoked in past month grouped as <20/day and >20/day.
g: Body mass index (BMI) = weight (lbs) / [height (in.)]^{1.5}; range 0.19–0.54.
h: Education grouped as <17 yrs and >17 yrs.

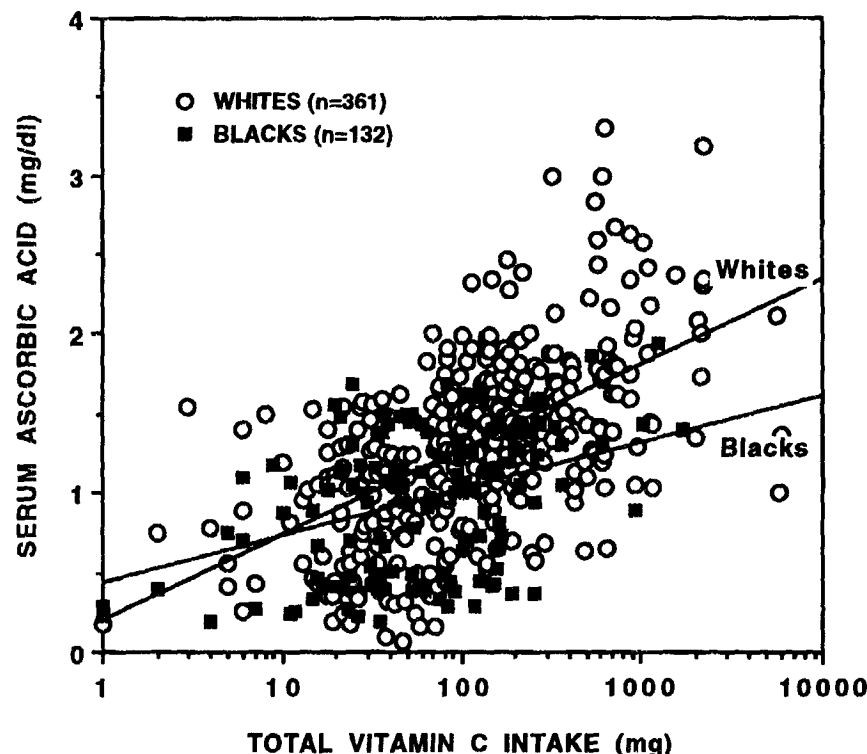


Figure 4. Scatter plot of vitamin C intake and serum ascorbic acid for whites and blacks and unadjusted predicted lines.

explained 0.041 of the R^2 . For a 10-fold increase in vitamin C intake, the serum AA in white women increased by 0.40 mg/dl, whereas in black women the increase was only 0.18 mg/dl.

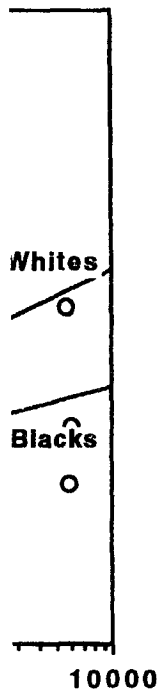
The other variables in Table 4 were significant predictors of serum AA but added ≤ 0.02 to the total R^2 . A variable that identified supplement users and non-supplement users appeared to be predictive of serum AA, even though the total intake of vitamin C included supplements. This might be explained by possible underassignment of supplemental vitamin C amounts where vitamin intake information was incomplete, underreporting of supplemental vitamin C intake among supplement users, or unexplained effects that covary with supplement use.

Smoking intensity in the last month and BMI were negatively associated with serum AA. Age and education also influenced serum AA, with higher levels of AA in older and highly educated women. Other variables, such as seasonality, day and time of blood draw, hours since last meal, and medication taken in the last month, were not significant determinants of serum AA.

Discussion

The distribution of serum AA in the control subjects in this study was similar to that reported for women in NHANES II (17). This similarity gives some confidence that the serum AA values in this control population are comparable to a national sample and suggests very little, if any, loss of AA during the stabilization and storage conditions used in this study.

At present, there is little consistency among studies in defining vitamin supplement users, time frame when the vitamin supplement was used, and the types of supplements that were used, thus making cross comparison of results difficult. In this study, 34% of women reported taking supplements containing vitamin C, which included multivitamins, in the month before blood was drawn and 46% reported consuming them "regularly" at some time in the last 20



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years. Subar and Block (2) reported that 28.8% of white women and 17.4% of black women were taking supplements daily, as reported by the 1987 HIS. Other studies report that >40% of elderly people took vitamin C daily (18,19) and 33.6% of women ≥ 18 years of age consumed vitamin C supplements at least once in the two-week period preceding the HIS interview (20).

If vitamin C from supplement source is not included in the total intake, then subjects can be misclassified. For usual intake, 9% of subjects who were ranked in the first quartile by diet alone were ranked in a higher quartile when diet plus supplemental vitamin C was used. Misclassification, especially if the first quartile is the referent group, can alter any effect of vitamin C that may be present.

Usual and recent supplemental vitamin C intake, when added to the respective dietary vitamin C intake, improves the correlation between these two forms of nutrient estimation. Not surprisingly, the correlation between usual and recent dietary vitamin C intake was low. One 24-hour recall is not representative of an individual's usual diet. For vitamin C, 7-14 days may be needed for an accurate estimate (21). However, adding supplement information obtained at the same time as the FFQ and 24-hour recall substantially improved the correlation between the two estimates of total vitamin C intake. Furthermore our data indicate that a measure of total vitamin C intake from diet and supplement improves the correlation between intake and serum levels for usual and recent intakes.

The importance of using total vitamin C intake is further underscored when the contribution of vitamin C from the diet and supplements is examined within quartiles of serum AA. The usual dietary intake of vitamin C is not predictive of the serum AA. The usual supplement intake information even by itself is much more predictive of the serum level than the usual dietary vitamin C intake alone. With the total measure of dietary and supplemental vitamin C, there is a good dose-response curve for the quartiles of serum AA.

There is a dose-response relationship between serum AA and recent dietary vitamin C estimate from foods consumed in the 24 hours before blood was drawn. This is not surprising, inasmuch as vitamin C is a water-soluble vitamin and recent intake is likely to be reflected in the blood taken close in time. Moreover, when total vitamin C from recent diet and supplements is examined, the dose response is striking. There is little difference in absorption or biologic activity of vitamin C, whether it is from diet or supplements (22). Therefore, to obtain a true estimate of vitamin C intake of individuals, an integrated approach is warranted in epidemiological studies. Rather than separate analyses of dietary and supplemental sources, total vitamin C intake should be used to rank subjects. In support of this view, Mares-Perlman and associates (23) state that "the high prevalence of supplement use emphasizes the importance of considering this source of nutrients in future investigations in which dietary intake is measured."

There are, however, potential problems with integration of dietary and supplemental sources of vitamins in epidemiological studies (9). Supplement users tend to have healthier dietary and life-style habits than non-supplement users. Another difficulty is that supplement use can easily change, and many people start taking these when they begin to feel ill. A further problem is that formulations of supplements change over time; thus, studies need to update data bases, such that recent and usual, as well as past, consumption of supplements can be analyzed in case-control and cohort studies.

In this investigation, nevertheless, the major determinant of serum AA and the variable that explains most of the variance in this population was found to be total recent vitamin C intake. As total vitamin C intake increased, serum levels rose. However, race appeared to play a role in the amount of increase in serum AA per gram of vitamin C consumed. Black women exhibit a lower level of serum AA for the same quantity of vitamin C intake than white women. This may be due to overestimation of vitamin C intake from the diet and supplements for black women. One explanation for inaccurate estimates of dietary vitamin C in the black population may be large discrepancies in vitamin C values in nutrient

data bases of food items such as cooked greens (24). With use of newer analytic methods, such as high-performance liquid chromatography (25), the vitamin C values obtained for cooked greens is about one-fifth the amount published by the US Department of Agriculture (26). Cooked greens contribute >10% of dietary vitamin C for blacks (27), and if the discrepancy in the actual value is true, then the impact is likely to be much higher for the black than for the white population. There may be other such foods that are consumed more often in racial or cultural lines. Such racial difference in dietary assessment needs to be investigated further.

Other variables, such as the indicator variable for supplement use, smoking intensity, BMI, age, and education, explain only small amounts of variance (1–2%) in the regression analysis. Even though the total intake included supplements, there appears to be an additional significant variable that identifies supplement users and nonusers. This term may be encompassing some of the unmeasured healthy life-style factors associated with supplement use (28,29).

The decrease in blood AA with smoking is well documented (30–33) and may be a reflection of defense mechanisms against free radicals derived from cigarette smoke. High BMI is negatively associated with serum AA, which suggests that women with greater body mass may need more vitamin C to attain the same serum level as those with lower body mass. This finding has been reported previously for vitamins C and E (18,34–37).

In conclusion, the correlation between serum AA and recent vitamin C intake at the time blood was drawn is higher than for usual dietary intake estimated from the FFQ. A total index of vitamin C intake substantially improves the correlation with serum AA. The main predictors of serum AA in this population were total recent vitamin C intake and race, and minor predictors were indicator of supplement use, smoking intensity, BMI, age, and education. Total vitamin C intake from supplements and foods may help in ranking individuals for serum AA and can be useful in epidemiological studies.

Acknowledgments and Notes

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